INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	25 OCT 2005
Applicant's or agent's file reference PS-5 PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US04/42016	13 December 2004 (13.12.2004)	12 December 2003 (12.12.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): B01L 3/02 and US Cl.: 422/100, 99; 436/180; 73/863.32, 864, 864.01

Applicant

PARAALLEL SYNTHESIS TECHNOLOGIES, INC.

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	13 September 2005 (13.09.2005)	Brian Gordon DEBORAH A. THOMAS PARALEGAL SPECIALIST ~~GROUP 1500~~ Telephone No. (571) 272-1700

Form PCT/ISA/237 (cover sheet) (April 2005)

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
   - ☒ paid additional fees
   - ☐ paid additional fees under protest and, where applicable, the protest fee
   - ☐ paid additional fees under protest but the applicable protest fee was not paid
   - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-20

INTERNATIONAL SEARCHING AUTHORITY

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 4-5, 9-21	YES
	Claims 1-3 and 6-8	NO
Inventive step (IS)	Claims 4-5, 9-21	YES
	Claims 1-3 and 6-8	NO
Industrial applicability (IA)	Claims 1-21	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claim 19 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 19 indefinite for the following reason(s): Claim 19 recites "such that the apertures are in axial alignment with one another". It is unclear what "the apertures" are referencing.

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:
Claims 1-3, 6-8 lack novelty under PCT Article 33(2) as being anticipated by Yang et al. US 2002/0094304 A1.

Yang et al. disclose an apparatus for dispensing a liquid includes a dispensing end, an adaptor end, and an elongate dispenser body extending therebetween. The dispenser body has a first major surface extending to the dispening end. The dispenser body defines a fluid reservoir opening on the first major surface for receiving a fluid to be dispensed. The dispenser body also defines a first elongate open channel opening on the first major surface and extending between the fluid reservoir and the free end of the dispenser body. The first channel includes dimensions such that the fluid to be dispensed is conducted through the channel by capillary action (abstract, see figures).

FIG. 1 depicts a dispensing pen 10 of the present invention. Pen 10 includes a dispensing end 12, an opposed adaptor end 14, and an elongate pen body 16 extending therebetween. Pen 10 is particularly suited to dispense spots of sub-nanoliter volumes of DNA or biomolecules to create microarrays for use in high-through-put analysis.

Fluid channel 24 and fluid reservoir 22 desirably hold in the range of about 5 to about 100 nanoliters and may be formed to hold about 60 nanoliters of fluid sample. The volume of fluid retained by pen 10 is desirably sufficient to deposit about 100 spots of the fluid onto a substrate between loadings. Pen 10 has demonstrated forming spots of fluid in the range of about 50 to about 500 picoliter having a diameter in the range of about 50 to about 200 microns. For present purposes, the spots of fluid dispensed by pen 10 desirably include about 100 picoliters of sample fluid having a diameter of about 120 microns. The dimensions and capacity of pen 10 are contemplated for all of the dispense pens of the present invention.

Claims 1-3, 6-8 lack novelty under PCT Article 33(2) as being anticipated by Martinsky US 6,101,946.

Martinsky discloses a device for fabricating microarrays of biochemical substances, consisting of a holder and one or more printing pins. The holder contains apertures with regular spacing that define the location of one or more printing pins during the printing process. The tip of each printing pin contains a sample channel that holds a predetermined volume of biological or chemical sample and a point that is machined to precision with an electronic discharge machine (EDM). The device can be attached to a motion control system for precise and automated movement in three dimensions. The flat tips of the pins are immersed in a biochemical sample such that a predefined volume of sample fills the sample channel of each pin. The holder and pins are then moved in proximity to a printing substrate whereby direct contact between the flat tips of the pins and the surface results in the transfer of a small amount of the sample onto the solid surface. The holder and pins are mass produced at high precision to ensure that the printed elements in the resultant microarray contains approximately the same quantity of sample. In one preferred embodiment, the device is employed to manufacture arrays of nucleic acids or derivatives thereof (abstract).

The pin is comprised of two parts: the shaft 28 and the collar 24. The shaft 28 is made out of 440-C stainless steel; Series

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

400 stainless is preferable to softer grades of stainless steel, such as series 300 materials which tend to be less durable than series 400 materials. Located on the lower, printing end of the shaft 28 is the point 20 of the pin. The point 20 of the pin is magnified in FIG. 3B to reveal a flat tip 32 and a sample channel 22. Referring again to FIG. 3A, the collar 24 is made out of 303 stainless steel and is located at the upper, non-printing end of the

The adjustment of the pin gap 30, shown in FIG. 3B, employs high precision tooling to hold the pin firmly and without damaging it (tapering of channel).

A reservoir 40 may also be incorporated within the device as seen in figure 4.

The invention employs custom sample channels that can be modified to hold sample volumes up to 1.0-2.0 microliters (1.0-2.0 X 10^{-6} liter). The capacity to use EDM to adjust the predefined volume of sample loaded allows the user to dictate the number of microarrays produced from a single loading. A typical pin, depicted in FIGS. 2A-2D, 3A, and 3B, will deposit approximately 1.0 nanoliter (1.0 X 10^{9} liter) of biochemical sample, providing for approximately 200 microarrays for a sample channel 22 that holds 0.2 microliters (0.2 X 10^{-6} liter). Larger sample channels that contain an expanded sample reservoir 40, as shown in FIG. 4, would allow as many as 1,000 microarrays to be produced from a single loading.

Other embodiments of the present invention allow for larger printing points that deliver up to 10 nanoliters (10 X 10^{-9} liter) of biochemical substance. This is accomplished by altering the EDM cutting routine used to make the points. A point that has square outer dimensions of 3 mil.times.3 mil (0.003".X 0.003") will produce a circular microarray element that is approximately 4 mil (0.004") in diameter. A point that has square outer dimensions of 8 mil X 8 mil (0.008" X 0.008") will produce a circular microarray element that is approximately 10 mil (0.010") in diameter.

It would have been obvious to one of ordinary skill in the art at the of the invention to coat the pins of Yang et al., Martinsky, or Davies et al. with silicon as taught by Gilbert to ensure the channels are sealed.

Claims 4-5, and 9-21 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest do not disclose the pin as being coated by Silicon, the tip having an non-flat surface, the pin has an external wall and grooves provided on the external wall leading to the channel for detecting any excess liquid wetting to the external wall to the channels.

The prior art does not teach or fairly suggest a pin for depositing a liquid on a substrate, the pin comprising: a printing tip at a first end thereof; a reservoir communicating with the printing tip, the pin having a thinned printing tip portion and a non-thinned remainder portion, including the reservoir, that is thicker than the thinned printing tip portion; a stepped portion between the thinned printing tip and the reservoir formed by the change in the thickness between the thinned printing tip and the non-thinned remainer portion; and a channel extending between the reservoir to the printing tip for delivering the liquid from the reservoir to the printing tip.

The prior art does not teach or fairly suggest a first planar member; a first aperture extending through the planar member for receiving a pin that deposits a predetermined volume of a liquid on a substrate to produce the microarray; and an elastomeric member provided at a distance above the first planar member, wherein the holder is microfabricated from a material selected from the group consisting of semiconductors, polymers, ceramics, and non-ferric alloys.

Claims 1-21 meet the criteria set out in PCT Article 33(4), and thus meet industrial applicability because the subject matter claimed can be made or used in industry.